

***Amendments to the Claims:***

This listing of the claims replaces all prior versions of the claims in the application:

**Listing of the Claims:**

1. (currently amended) A penetrating module comprising a penetrating peptide and an effector that is coupled or fused to said penetrating peptide, said penetrating peptide consisting of at least one amino acid sequence selected from the group consisting of:

- a) SEQ ID NOS: 1-15;
- b) SEQ ID NOS: ~~24-29~~ 25-29 and;
- c) at least 12 contiguous amino acids of any of the peptides in a) or b),

wherein said penetrating peptide is capable of translocating the effector across a biological barrier, wherein, when the effector is a polypeptide, the penetrating module is encoded by a chimeric gene sequence.

2-14. (canceled)

15. (previously presented) The penetrating module of claim 1, wherein said effector is a bioactive peptide.

16. (previously presented) The penetrating module of claim 15, wherein said bioactive peptide is selected from the group consisting of: insulin, growth hormone, a gonadotropin, a growth factor, erythropoietin, granulocyte/monocyte colony stimulating factor (GM-CSF),  $\alpha$ MSH, enkephalin, dalargin, kyotorphin, EPO, bFGF, hirulog, a lutenizing hormone releasing hormone (LHRH) analog, and neurotrophic factors.

17. (previously presented) The penetrating module of claim 1, wherein said effector is a pharmaceutically active agent.

18. (previously presented) The penetrating module of claim 17, wherein said pharmaceutically active agent is selected from the group consisting of: an anticoagulant, a toxin, an antibiotic, an antipathogenic agent, an antigen, an antibody fragment, an

immunomodulator, a vitamin, an enzyme, an antineoplastic agent, heparin, methotrexate and a therapeutic agent.

19. (withdrawn) A method of translocating the penetrating module of claim 1 across a biological barrier, the method comprising introducing the penetrating module to a biological barrier.

20. (withdrawn) A method of translocating the penetrating module of claim 10 across a biological barrier, the method comprising introducing the penetrating module to a biological barrier.

21-25. (canceled)

26. (previously presented) The penetrating module of claim 1, wherein translocation across a biological barrier occurs within a tissue selected from the group consisting of: epithelial cells and endothelial cells.

27. (previously presented) The penetrating module of claim 1, wherein said biological barrier is selected from the group consisting of: tight junctions and the plasma membrane.

28-30. (canceled)

31. (previously presented) A pharmaceutical composition comprising a therapeutically or prophylactically effective amount of the penetrating module of claim 1, and a pharmaceutically acceptable carrier.

32. (original) The pharmaceutical composition of claim 31, wherein the composition further comprises a mixture of at least two substances selected from the group consisting of a non-ionic detergent, an ionic detergent, a protease inhibitor; and a reducing agent.

33. (original) The pharmaceutical composition of claim 32, wherein the non-ionic detergent is a poloxamer.

34. (previously presented) The pharmaceutical composition of claim 33, wherein the poloxamer is polyoxyethylene-polyoxypropylene Block Copolymer.
35. (original) The pharmaceutical composition of claim 32, wherein the ionic detergent is a bile salt.
36. (previously presented) The pharmaceutical composition of claim 35, wherein the bile salt is Taurodeoxycholate.
37. (previously presented) The pharmaceutical composition of claim 32, wherein the protease inhibitor is selected from the group consisting of aprotinin and soy bean trypsin inhibitor.
38. (previously presented) The pharmaceutical composition of claim 32, wherein the reducing agent is N-Acetyl-L-cystein (NAC).
39. (withdrawn) A method of producing the penetrating module of claim 1, said method comprising coupling said effector to said penetrating peptide.
40. (withdrawn) The method of claim 39, wherein the coupling of said effector to said penetrating peptide is achieved by a covalent bond.
41. (withdrawn) The method of claim 40, wherein said covalent bond is a peptide bond.
42. (withdrawn) The method of claim 40, wherein the covalent bond is achieved by a homo- or a hetero-functional bridging reagent.
43. (withdrawn) The method of claim 42, wherein the bridging reagent is a succinimidyl-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC)-type reagent.

44. (withdrawn) The method of claim 40, wherein the covalent bond is achieved by a peptide linker.

45. (withdrawn) The method of claim 44, wherein the peptide linker has the sequence of SEQ ID NO: 16 or SEQ ID NO:17.

46. (withdrawn) The method of claim 44, wherein the peptide linker can be cleaved by an enzyme.

47. (withdrawn) The method of claim 46, wherein the peptide linker is designed to be cleaved by an enzyme conditionally activated under a certain physiological state and wherein the released effector favorably influences said physiological state.

48. (withdrawn) The method of claim 39, wherein the coupling of said effector to said penetrating peptide is achieved by a non-covalent bond.

49. (withdrawn) The method of claim 48, wherein the non-covalent bond is achieved by an attachment of a hydrophobic moiety to the penetrating peptide, wherein the hydrophobic moiety enables the penetrating peptide to be incorporated at the interface of a hydrophobic vesicle in which the effector is contained.

50. (withdrawn) The method of claim 48, wherein the non-covalent bond is the result of a biotin-avidin or biotin-streptavidin interaction.

51-52. (canceled)

53. (previously presented) A kit for treating a disease or pathological condition comprising, in one or more containers, a therapeutically or prophylactically effective amount of the pharmaceutical composition of claim 31.

54. (withdrawn) A method of treating or preventing a disease or pathological condition, said method comprising administering to a subject in which such treatment or prevention is

desired, the pharmaceutical composition of claim 31, in an amount sufficient to treat or prevent said disease or said pathological condition in said subject.

55. (withdrawn) The method of claim 54, wherein said disease or said pathological condition is selected from a group consisting of endocrine disorders, diabetes, infertility, hormone deficiencies, osteoporosis, neurodegenerative disorders, Alzheimer's disease, Parkinson's disease, Huntington's disease, cardiovascular disorders, atherosclerosis, hypercoagulable states, hypocoagulable states, coronary disease, cerebrovascular events, metabolic disorders, obesity, vitamin deficiencies, haematological disorders, and neoplastic disease.

56. (withdrawn) A method for producing the penetrating module of claim 1 comprising

- transfecting a production cell with a vector comprising a nucleic acid molecule of a fusion protein encoding said penetrating peptide and an effector operably linked to an expression control sequence;
- culturing said production cell under conditions that permit production of a fusion protein consisting of the penetrating peptide and an effector peptide; and
- isolating said fusion protein.

57-62. (canceled)

63. (withdrawn) The penetrating module of claim 1, wherein said penetrating peptide is derived from a human neurokinin receptor, and is characterized by the ability to penetrate biological barriers *in vivo*.

64-67. (canceled)

68. (previously presented) The penetrating module of claim 1, further comprising a molecular vessel selected from the group consisting of a soluble receptor, a minireceptor, and a binding protein, wherein said penetrating peptide is coupled or fused to the molecular vessel, which encloses the effector.

69. (original) The penetrating module of claim 68, wherein the soluble receptor is a soluble insulin receptor.
70. (original) The penetrating module of claim 69, wherein the effector is insulin.
71. (original) The penetrating module of claim 68, wherein the minireceptor is the ligand-binding domain of the insulin receptor.
72. (original) The penetrating module of claim 71, wherein the effector is insulin.
73. (original) The penetrating module of claim 68, wherein the binding protein is Intrinsic factor.
74. (original) The penetrating module of claim 73, wherein the effector is vitamin B12.
75. (previously presented) A pharmaceutical composition comprising a therapeutically or prophylactically effective amount of the penetrating module according to claim 68, and a pharmaceutically acceptable carrier.
76. (withdrawn) A method for producing the penetrating module of claim 1 comprising using solid-phase peptide synthesis.
77. (previously presented) The penetrating module of claim 15, wherein the bioactive peptide further comprises a chemical modification.
78. (previously presented) The penetrating module of claim 77, wherein said chemical modification comprises the attachment of one or more polyethylene glycol residues to the bioactive peptide.
79. (withdrawn) The method of claim 56, wherein the fusion protein is further chemically modified.

80. (withdrawn) The method of claim 79, wherein the chemical modification comprises the attachment of one or more polyethylene glycol residues to the fusion protein.

81. (currently amended) A penetrating module comprising a penetrating peptide and an effector that is coupled or fused to said penetrating peptide, said penetrating peptide consisting of at least one amino acid sequence selected from the group consisting of:

- a) SEQ ID NOS: 1-15; and
- b) SEQ ID NOS: 24-29,

wherein said penetrating peptide is capable of translocating the effector across a biological barrier, wherein, when the effector is a polypeptide, the penetrating module is encoded by a chimeric gene sequence.

82. (withdrawn) A penetrating module comprising a penetrating peptide and an effector that is coupled or fused to said penetrating peptide, said penetrating peptide comprising at least one amino acid sequence selected from the group consisting of:

- a) SEQ ID NOS: 25-29 and;
- b) at least 12 contiguous amino acids of any of the peptides in a),

wherein said penetrating peptide is capable of translocating across a biological barrier.

83. (withdrawn) A penetrating module comprising a penetrating peptide and an effector that is coupled or fused to said penetrating peptide, said penetrating peptide comprising at least one amino acid sequence selected from the group consisting of SEQ ID NOS: 25-29, wherein said penetrating peptide is capable of translocating across a biological barrier.

84. (New) The penetrating module of claim 1, wherein the effector is covalently bound to the penetrating peptide.

85. (New) The penetrating module of claim 84, wherein the effector is selected from the group consisting of: insulin, growth hormone, a gonadotropin, a growth factor, erythropoietin, granulocyte/monocyte colony stimulating factor (GM-CSF),  $\alpha$ MSH, enkephalin, dalargin, kyotorphin, EPO, bFGF, hirulog, a lutenizing hormone releasing hormone (LHRH) analog, and neurotrophic factors.

86. (New) The penetrating peptide of claim 84, wherein said effector is a pharmaceutically active agent.

87. (New) The penetrating peptide of claim 86, wherein said pharmaceutically active agent is selected from the group consisting of: an anticoagulant, a toxin, an antibiotic, an antipathogenic agent, an antigen, an antibody fragment, an immunomodulator, a vitamin, an enzyme, an antineoplastic agent, and a therapeutic agent.

88. (New) The penetrating module of claim 1, wherein the effector is ionically bound to the penetrating peptide.

89. (New) The penetrating module of claim 88, wherein the effector is selected from the group consisting of: insulin, growth hormone, a gonadotropin, a growth factor, erythropoietin, granulocyte/monocyte colony stimulating factor (GM-CSF),  $\alpha$ MSH, enkephalin, dalargin, kyotorphin, EPO, bFGF, hirulog, a lutenizing hormone releasing hormone (LHRH) analog, and neurotrophic factors.

90. (New) The penetrating peptide of claim 88, wherein said effector is a pharmaceutically active agent.

91. (New) The penetrating peptide of claim 90, wherein said pharmaceutically active agent is selected from the group consisting of: an anticoagulant, a toxin, an antibiotic, an antipathogenic agent, an antigen, an antibody fragment, an immunomodulator, a vitamin, an enzyme, an antineoplastic agent, and a therapeutic agent.

92. (New) A penetrating module consisting of a penetrating peptide and an effector that is coupled or fused to said penetrating peptide, said penetrating peptide consisting of at least one amino acid sequence selected from the group consisting of:

- a) SEQ ID NO: 24 and;
- b) at least 12 contiguous amino acids of any of SEQ ID NO:24,



wherein said penetrating peptide is capable of translocating the effector across a biological barrier, wherein, when the effector is a polypeptide, the penetrating module is encoded by a chimeric gene sequence.

93. (previously presented) The penetrating module of claim 92, wherein said effector is a bioactive peptide.

94. (previously presented) The penetrating module of claim 93, wherein said bioactive peptide is selected from the group consisting of: insulin, growth hormone, a gonadotropin, a growth factor, erythropoietin, granulocyte/monocyte colony stimulating factor (GM-CSF),  $\alpha$ MSH, enkephalin, dalargin, kyotorphin, EPO, bFGF, hirulog, a lutenizing hormone releasing hormone (LHRH) analog, and neurotrophic factors.

95. (previously presented) The penetrating module of claim 92, wherein said effector is a pharmaceutically active agent.

96. (previously presented) The penetrating module of claim 95, wherein said pharmaceutically active agent is selected from the group consisting of: an anticoagulant, a toxin, an antibiotic, an antipathogenic agent, an antigen, an antibody fragment, an immunomodulator, a vitamin, an enzyme, an antineoplastic agent, heparin, methotrexate and a therapeutic agent.

97. (previously presented) The penetrating module of claim 92, wherein translocation across a biological barrier occurs within a tissue selected from the group consisting of: epithelial cells and endothelial cells.

98. (previously presented) The penetrating module of claim 92, wherein said biological barrier is selected from the group consisting of: tight junctions and the plasma membrane.

99. (previously presented) A pharmaceutical composition comprising a therapeutically or prophylactically effective amount of the penetrating module of claim 92, and a pharmaceutically acceptable carrier.

100. (original) The pharmaceutical composition of claim 99, wherein the composition further comprises a mixture of at least two substances selected from the group consisting of a non-ionic detergent, an ionic detergent, a protease inhibitor; and a reducing agent.

101. (original) The pharmaceutical composition of claim 100, wherein the non-ionic detergent is a poloxamer.

102. (previously presented) The pharmaceutical composition of claim 101, wherein the poloxamer is polyoxyethylene-polyoxypropylene Block Copolymer.

103. (original) The pharmaceutical composition of claim 100, wherein the ionic detergent is a bile salt.

104. (previously presented) The pharmaceutical composition of claim 103, wherein the bile salt is Taurodeoxycholate.

105. (previously presented) The pharmaceutical composition of claim 100, wherein the protease inhibitor is selected from the group consisting of aprotinin and soy bean trypsin inhibitor.

106. (previously presented) The pharmaceutical composition of claim 100, wherein the reducing agent is N-Acetyl-L-cystein (NAC).

107. (previously presented) A kit for treating a disease or pathological condition comprising, in one or more containers, a therapeutically or prophylactically effective amount of the pharmaceutical composition of claim 99.

108. (previously presented) The penetrating module of claim 92, further comprising a molecular vessel selected from the group consisting of a soluble receptor, a minireceptor, and a binding protein, wherein said penetrating peptide is coupled or fused to the molecular vessel, which encloses the effector.

109. (original) The penetrating module of claim 108, wherein the soluble receptor is a soluble insulin receptor.
110. (original) The penetrating module of claim 109, wherein the effector is insulin.
111. (original) The penetrating module of claim 108, wherein the minireceptor is the ligand-binding domain of the insulin receptor.
112. (original) The penetrating module of claim 111, wherein the effector is insulin.
113. (original) The penetrating module of claim 108, wherein the binding protein is Intrinsic factor.
114. (original) The penetrating module of claim 113, wherein the effector is vitamin B12.
115. (previously presented) A pharmaceutical composition comprising a therapeutically or prophylactically effective amount of the penetrating module according to claim 108, and a pharmaceutically acceptable carrier.
116. (previously presented) The penetrating module of claim 93, wherein the bioactive peptide further comprises a chemical modification.
117. (previously presented) The penetrating module of claim 116, wherein said chemical modification comprises the attachment of one or more polyethylene glycol residues to the bioactive peptide.
118. (New) The penetrating module of claim 92, wherein the effector is covalently bound to the penetrating peptide.
119. (New) The penetrating module of claim 118, wherein the effector is selected from the group consisting of: insulin, growth hormone, a gonadotropin, a growth factor, erythropoietin,

granulocyte/monocyte colony stimulating factor (GM-CSF),  $\alpha$ MSH, enkephalin, dalargin, kyotorphin, EPO, bFGF, hirulog, a lutenizing hormone releasing hormone (LHRH) analog, and neurotrophic factors.

120. (New) The penetrating peptide of claim 118, wherein said effector is a pharmaceutically active agent.

121. (New) The penetrating peptide of claim 120, wherein said pharmaceutically active agent is selected from the group consisting of: an anticoagulant, a toxin, an antibiotic, an antipathogenic agent, an antigen, an antibody fragment, an immunomodulator, a vitamin, an enzyme, an antineoplastic agent, and a therapeutic agent.

122. (New) The penetrating module of claim 92, wherein the effector is ionically bound to the penetrating peptide.

123. (New) The penetrating module of claim 122, wherein the effector is selected from the group consisting of: insulin, growth hormone, a gonadotropin, a growth factor, erythropoietin, granulocyte/monocyte colony stimulating factor (GM-CSF),  $\alpha$ MSH, enkephalin, dalargin, kyotorphin, EPO, bFGF, hirulog, a lutenizing hormone releasing hormone (LHRH) analog, and neurotrophic factors.

124. (New) The penetrating peptide of claim 122, wherein said effector is a pharmaceutically active agent.

125. (New) The penetrating peptide of claim 124, wherein said pharmaceutically active agent is selected from the group consisting of: an anticoagulant, a toxin, an antibiotic, an antipathogenic agent, an antigen, an antibody fragment, an immunomodulator, a vitamin, an enzyme, an antineoplastic agent, and a therapeutic agent.